

Figure: Lung function data according to the GLI-2012 ethnic-specific reference equations. Data from South Asian children were expressed according to the 'Black' Equation. The "other" group comprise children of "mixed ethnic backgrounds" and those not covered by the other 3 groups.

Abstract S33 Figure 1

Abstract S34 Table 1 Comparison of Lung Function: Children with SCD vs. healthy Black controls.

	Baseline Mean (95% CI) Diff (SCD – Health)	Bronchodilator Response Mean (95% CI) Diff (SCD–Health)
Resistance at 10Hz Z Score <sup>[2]</sup>	–0.2 (–0.4; 0.1)	0.3 (–0.2; 0.7)
sReff Z Score <sup>[3]</sup>	–0.3 (–0.6; 0.1)	0.5 (0.1; 0.8)
TLC Z Score <sup>[4]</sup>	–0.8 (–1.1; –0.5)*	
FVC Z Score <sup>[5]</sup>	–1.0 (–1.2; –0.7)*	0.2 (–0.1; 0.5)
FEV1 Z Score <sup>[6]</sup>	–1.2 (–1.5; –0.9)*	0.2 (–0.1; 0.5)

\*p<0.001.

### S35 DIFFERENT EARLY LIFE FACTORS ARE IMPORTANT IN THE DEVELOPMENT OF ATOPIC AND NON-ATOPIC ASTHMA

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<sup>1</sup>E Petley, <sup>2</sup>KC Pike, <sup>3</sup>HM Inskip, <sup>4</sup>KM Godfrey, <sup>2</sup>JSA Lucas, <sup>4</sup>G Roberts, <sup>3</sup>Southampton Women's Survey Study Group. <sup>1</sup>Clinical and Experimental Sciences, University of

Southampton Faculty of Medicine, Southampton, UK; <sup>2</sup>NIHR Southampton Respiratory Biomedical Research Unit, Southampton University Hospitals Trust, Southampton, UK; <sup>3</sup>Southampton Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK; <sup>4</sup>Human DevelopmentHealth, University of Southampton Faculty of Medicine, Southampton, UK

**Background** Many factors have been related to the development of childhood asthma but there is inconsistency between studies.

**Objective** To understand how early life factors are linked to the development of the various asthma phenotypes at age 6 years in the Southampton Women's Survey (SWS) children's cohort.

**Methods** Data was collected from 940 children and their parents, primarily through questionnaires during pregnancy and at 6m, 1, 3 and 6 years. Prevalent asthma was defined by a doctor's diagnosis and a wheezing episode in the last year. Data was analysed using STATA v9. A relative risk analysis using a univariate approach was undertaken, followed by a multivariate analysis.

**Results** Both maternal (RR=1.61, p=0.041) and paternal (RR=2.05, p=0.002) atopic disease increased the risk of asthma at age 6 years. The risk increased with atopy, defined as a positive skin prick test, at 3 years (RR=3.05, p<0.001) and with wheeze in the first 3 years (RR=8.79, p<0.001). Episodes of bronchiolitis and chest infections were associated, in a dose-dependent manner, with the risk of asthma (RR=1.50, p=0.022). Predictors in the multivariate model were wheeze in the first 3 years (RR=10.74, p<0.001), atopy (RR=2.87, p<0.001) and maternal atopy (RR=2.22, p=0.011). When asthma at age 6 years was split into atopic and non-atopic asthma, the predictors were very different. Atopic asthma was associated with paternal atopy (RR=4.13, p=0.002), male sex (RR=2.56, p=0.030), atopy at 3 years (RR=10.31, p<0.001) and wheeze in the first 3 years (RR=5.91, p=0.004). In the multivariate analysis, the following were predictive: wheeze in the first 3 years (RR=13.55, p=0.012), atopy at 3 years (RR=10.13, p<0.001), paternal atopy (RR=2.97, p=0.017) and a 12 month infant dietary pattern that follows current guidelines (RR=1.79, p=0.016). For non-atopic asthma, bronchiolitis or chest infections (RR=1.76, p=0.047), wheeze in the first 3 years (RR=20.69, p=0.003) and tobacco smoke exposure at 6 years (RR=2.16, p=0.035) increased the risk. Only wheeze in the first 3 years remained in the multivariate model.

**Conclusions** Different hereditary and early life factors modify the risk of atopic and non-atopic asthma at 6 years of age. This suggests that these two asthma phenotypes have different pathophysiologies.

## Pathophysiology of pulmonary vascular remodelling

S36

### P38 MAPK: AN IMPORTANT PATHWAY IN THE PATHOBIOLOGY OF PULMONARY HYPERTENSION AND PULMONARY VASCULAR REMODELLING

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<sup>1</sup>AC Church, <sup>2</sup>R Wadsworth, <sup>3</sup>G Bryson, <sup>3</sup>DJ Welsh, <sup>1</sup>AJ Peacock. <sup>1</sup>Scottish Pulmonary vascular Unit, Glasgow, UK; <sup>2</sup>University of Strathclyde, Glasgow, UK; <sup>3</sup>University of Glasgow, Glasgow, UK

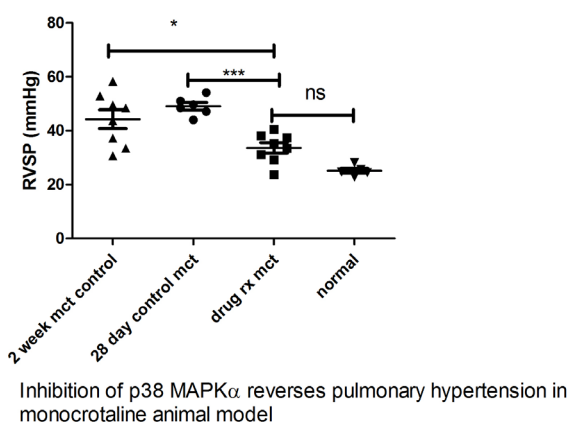
The p38 MAPK pathway is increasingly recognised as important in inflammation leading to systemic vascular disease but its role in pulmonary vascular disease is unclear. Our group has previously identified the p38MAPK $\alpha$  isoform to be critical in hypoxic-induced proliferation of pulmonary artery fibroblasts, a key step in the pathogenesis of pulmonary vascular remodelling. This study sought to investigate the role of p38MAPK in animal models of pulmonary hypertension and in human disease.

**Methods** Sprague Dawley rats were exposed to chronic hypoxia for 14 days and received a selective p38 MAPK $\alpha$  inhibitor from day 1

in a prevention strategy, or after 14 days in a treatment strategy. Both prevention and treatment methods were further employed in a second monocrotaline animal model. Haemodynamic measurements (right ventricular systolic pressure RVSP, right ventricular hypertrophy RVH) were performed, and lungs were removed for immunohistochemistry (IHC) and biochemical analysis. Multiplex ELISA was used to analyse cytokine profile in rat serum. Primary PAF were isolated and siRNA techniques employed to knockdown p38MAPK $\alpha$ . IHC for p38 MAPK $\alpha$  was performed on human tissue from patients with idiopathic pulmonary arterial hypertension.

**Results** siRNA to p38MAPK $\alpha$  inhibited the hypoxic induced proliferation of PAFs. Increased levels of total p38 MAPK activity and increased expression of the alpha isoform was found in the lungs of both chronic hypoxic and MCT animals compared to normal. Using the p38 MAPK inhibitor in the chronic hypoxic and monocrotaline *in vivo* prevention study resulted in lower RVSP and RVH in the drug treated animals ( $p < 0.005$ ). In the reversal study of both animal models the inhibitor reversed established pulmonary hypertension as determined by RVSP and RVH ( $p < 0.001$ ). Both serum and whole lung levels of IL-6 were lower in the drug treated animals compared to normal. Increased expression of p38 MAPK was observed in lungs from IPAH patients compared to control.

**Conclusions** Our study suggests p38 MAPK alpha is important in pulmonary hypertension. Inhibition of this pathway can prevent the development of PH and perhaps more clinically relevant, can reverse established disease *in vivo*. Reduction in IL-6 may be a mechanism underlying this process.



Abstract S36 Figure 1

### S37 CAN THE LUNG REVERSE REMODEL? GENE THERAPY FOR CARDIAC FAILURE ALTERS PULMONARY GENE EXPRESSION

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<sup>1</sup>JES Park, <sup>2</sup>AR Lyon, <sup>1</sup>L Hector, <sup>1</sup>MJD Griffiths. <sup>1</sup>Unit of Critical Care, NHLI, Imperial College, London, UK; <sup>2</sup>Department of Cardiovascular Medicine, NHLI, Imperial College, London, UK

**Introduction** Irreversible alveolar capillary membrane (ACM) remodelling accompanies chronic heart failure (CHF), contributing to dyspnoea, the predominant symptom that limits quality of life in CHF. Gene therapy is aimed at improving myocardial function in CHF. Restoration of Sarco-endoplasmic reticulum calcium ATPase (SERCA2a) gene expression in animal models of CHF restores haemodynamic parameters towards normal.

The lungs are the direct upstream target of raised left atrial pressure and hence pulmonary venous hypertension. We hypothesised that mechanical strain at the pulmonary micro vasculature associated with PVH up-regulates mediators leading to pulmonary inflammation and ACM remodelling. We have previously shown that gene expression of monocyte chemoattractant protein (MCP)-1,

interleukin(IL)-6, endothelin (ET)-1, endothelin receptors (ETR) A and B, and endothelial converting enzyme (ECE) are altered in the lungs of Sprague-Dawley rats at 16 weeks after left coronary artery ligation. We now sought to determine the effect of SERCA2a gene therapy on gene expression of these mediators in the lung.

**Methods** Gene expression of components of the ET-1 pathway, MCP-1 and IL-6 were investigated in whole lungs of rats at 16 weeks after LCA, at 16 weeks post LCA with tail vein injection of adeno-associated viral (AAV) gene transfer of SERCA2a at 12 weeks post LCA, or sham procedure ( $n=5$  in each group). Lungs were snap frozen in liquid nitrogen, RNA extracted using a modified Trizol and RN easy protocol and gene expression determined in reverse transcribed cDNA by qPCR.

**Results** Expression of ET-1, ETAR, MCP-1 and IL-6 genes were elevated in heart failure animals and reduced to or towards normal in SERCA2a treated animals. In heart failure animals there was a trend towards reduced ETRB expression which was significantly improved by SERCA2a gene therapy (figure 1). ECE gene expression was not altered by LCA or gene therapy.

**Conclusion** SERCA2a gene therapy directed at the myocardium in heart failure also affects gene expression in the lungs of CHF animals. This may provide therapeutic benefit to the lungs in addition, reducing inflammation and stimuli associated with structural and vascular remodelling.

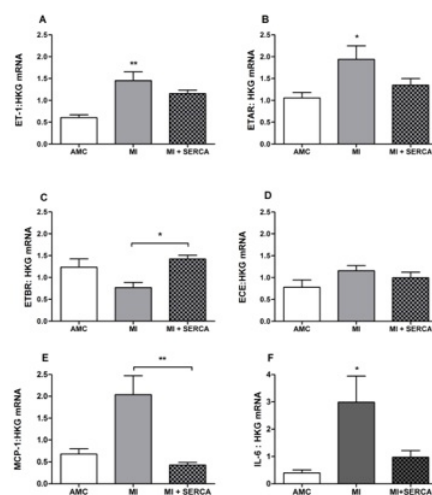


Figure 1 Effect of treatment with SERCA gene therapy on endothelin-1 (ET-1), endothelin receptor (ETR) a & b, endothelial converting enzyme (ECE), Monocyte chemoattractant protein (MCP)-1 and Interleukin (IL)-6 mRNA expression in chronic heart failure in the rat.

Abstract S37 Figure 1

### S38 TGF-BETA1 NEGATIVELY REGULATES BMP4 SIGNALLING IN HUMAN PULMONARY ARTERY SMOOTH MUSCLE CELLS VIA A SMAD3-DEPENDENT MECHANISM

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PD Upton, RJ Davies, T Tajsic, L Long, A Crosby, NW Morrell. University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom

**Introduction** BMP4 signals via the Smad pathway to induce the expression of the ID dominant-negative basic helix-loop-helix transcription factors (ID1-4) that regulate cell differentiation. We have shown that ID induction is blunted in human pulmonary artery smooth muscle cells (HPASMCs) from pulmonary arterial hypertension (PAH) patients with mutations in the bone morphogenetic type-II receptor (BMPRII). TGF $\beta$ 1 is implicated in the pathogenesis of PAH. We therefore examined whether TGF $\beta$ 1 and BMP4 signaling directly interact in HPASMCs.